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SCIENCE DIRECT

Free Radical Biology & Medicine 39 (2005) 1109 – 1116

www.elsevier.com/locate/freeradbiomed

Original Contribution

Inhibition of brain damage by edaravone, a free radical scavenger, can be monitored by plasma biomarkers that detect oxidative and astrocyte damage in patients with acute cerebral infarction ☆

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Received 11 May 2005; revised 3 June 2005; accepted 3 June 2005

Abstract

We assess the availability of plasma biomarkers to monitor the brain damage and the therapeutic efficacy of edaravone. The study consisted of 51 patients with ischemic cerebral infarcts. They were divided into 2 groups: GI ($n = 24$) had cortical lesions, and GII ($n = 27$) had lesions in the basal ganglia or brain stem. Edaravone was administered to 27 randomly selected patients (GIa, $n = 13$; GIIa, $n = 14$) and its efficacy was studied by comparing their plasma OxLDL, S-100B, and MnSOD levels to those in patients without edaravone (GIb, $n = 11$, GIIb, $n = 13$). Three days after the start of edaravone, plasma OxLDL was significantly lower in GIa than GIb patients (0.177 ± 0.024 ng/μg apoB vs 0.219 ± 0.026, $P < 0.05$). In GIIa patients, pre- and posttreatment plasma OxLDL was not significantly different (0.156 ± 0.013 vs 0.152 ± 0.020). In GIa patients, S-100B and MnSOD were significantly lower than in GIb patients ($P < 0.05$). The neurological condition at the time of discharge had recovered in GIa but not GIb patients. Ours is the first evidence to confirm the efficacy of edaravone by plasma biomarkers. In patients with cortical infarcts, edaravone reduced oxidative damage, thereby limiting the degree of brain damage.

Keywords: Acute cerebral infarction; Free radical scavenger; Plasma biomarker; Free radicals

Introduction

Upon energy failure during brain ischemia, polyunsaturated fatty acids are released from membrane phospholipids. This is followed by activation of the arachidonate cascade that includes the lipoxygenase pathway, the production of oxygen radicals, and lipid peroxidation, which is thought to contribute to neuronal injury [1–3].

Edaravone exerts antioxidant action that suppresses free radicals including hydroxy, peroxy, and alcoxy radicals; it has been used to treat patients with acute stroke [4]. Clinical and experimental studies [5–8] have shown that it exerts protective effects against oxidative actions. The neuroprotective efficacy of edaravone and its beneficial effect on functional outcomes have been demonstrated in patients with acute ischemic stroke [9]. However, the role of its antioxidant actions in its therapeutic effects remains to be elucidated. We previously reported that patients with atherothrombotic and cortical infarcts manifested significantly higher plasma oxidized low-density lipoprotein (OxLDL) levels than did patients with lacunar infarcts and

Abbreviations: OxLDL, oxidized low-density lipoprotein; NIHSS, NIH Stroke Scale; mAb, monoclonal antibody; SOD, superoxide dismutase; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; FLAIR, flow-sensitive alternating inversion recovery; IR, inversion-recovery; 8-OHdG, 8-hydroxydeoxyguanosine; MCAOR, middle cerebral artery occlusion/reperfusion.

☆ This research was supported by Grants-in-Aid for Research C2 (No. 17591516) from the Ministry of Education, Science, Sports, and Culture of Japan.

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doi:10.1016/j.freeradbiomed.2005.06.001

age-matched controls [10]. Plasma OxLDL levels were correlated with the infarct volume and the admission NIH Stroke Scale (NIHSS) score but not with the modified Rankin scale on discharge [11]. On the other hand, not all patients with severe large infarcts over the hemisphere had high plasma OxLDL levels and to some degree, the increased plasma OxLDL level at stroke onset was associated with expansion of the infarct size 3 days after the insult. Our results suggested that since increased plasma OxLDL reflects brain oxidative damage in patients with moderate cortical infarction and predicts the presence of salvageable regions, it is helpful to monitor OxLDL in stroke patients.

Protein S-100B, an acidic Ca^{2+}-binding protein (20 kDa) that comprises a major component of cytosol, exists predominantly in astrocytes and Schwarzman cells [12–14]. It is produced and released by astrocytes and can stimulate the activation of microglia and astrocytes, and it plays a pivotal role in the occurrence of delayed infarct expansion and prolonged suppression of neuronal functions in the peri-infarct area [15–17]. S-100B levels in cerebrospinal fluid or plasma are now used as a biomarker for evaluating the presence and severity of brain damage and to predict the prognosis after acute ischemic or traumatic brain injury [18]. In patients with acute ischemic stroke, serum S-100B levels correlate with infarct size and neurological and functional outcomes [19,20]. Therefore, S-100B levels may be useful for the evaluation of neuroprotective therapies [21].

To investigate whether its efficacy is reflected in the level of plasma biomarkers of brain damage, we compared plasma OxLDL and S-100B levels in ischemic stroke patients who did, or did not, receive edaravone. Here we first demonstrate that the therapeutic efficacy of edaravone can be monitored by plasma biomarkers that detect oxidative and astrocyte damage in acute cerebral infarction.

Methods

Subjects

Our study population consisted of 51 patients with ischemic cerebral infarcts. They were 31 men and 20 women, ranging in age from 40 to 82 years (67.1 ± 12.5, mean ± SD). The controls were 19 age-matched healthy volunteers who had no history of cerebrovascular accidents (9 men and 10 women, aged 61.2 ± 9.6 years, range 35–78). The patients had been admitted consecutively between February 2002 and July 2003 to the Stroke Care Unit at the University of Tokushima Hospital. Prior informed consent was obtained from all study participants or their relatives. Our study was approved by the ethics committee of the University of Tokushima.

All patients underwent magnetic resonance imaging (MRI) examination immediately at admission; echocardiography and extracranial duplex ultrasound were also performed in all patients. A diagnosis of stroke was based on clinical findings. An NIHSS [22,23] score was assigned at admission and discharge to determine neurological deficits. Baseline data (age, sex), conventional vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia), and previous atrial fibrillation were recorded. Patients whose pertinent data could not be evaluated at the time of stroke onset and those with hemorrhagic infarction were excluded from this study. Based on the location of the ischemic lesions [11], the patients were divided into two groups (Table 1 and Fig. 1A). In GI patients (n = 24), the infarct was located in cortical regions in the cerebral hemisphere and involved the frontal, parietal, and temporal lobe or the occipital lobe and cerebellum (Fig. 1A,a). In GII patients (n = 27), the infarct involved basal ganglia regions in the anterior circulation (putamen, caudate head), corona radiata, or brain stem and thalamus (Fig. 1A,b). The stroke subtypes were defined according to the TOAST classification system [23]. Of the 51 patients, 16 (31.4%) had cardioembolic, 13 (25.5%) had atherothrombotic, and 22 (43.1%) had lacunar infarcts. The atherothrombotic infarct group included patients with clinical and imaging findings of either significant stenosis or occlusion of a major artery or a branch of the cortical artery, presumably due to atherosclerosis. The cardioembolic infarct group included patients with arterial occlusion presumably due to an embolus arising in the heart. The lacunar infarction group included patients with one of the traditional clinical lacunar syndromes and no evidence of cerebral cortical dysfunction, and patients whose MRI did not show lesions exceeding 1.5 cm in diameter (Fig. 1A,b). Randomization was based on a computer-generated random number table; from this, a

Table 1
Characteristics of patients recruited in this study at admission

	Group I		Group II	
	GIa	GIb	GIIa	GIIb
Age	71.8 ± 6.9	60.1 ± 11.2	70.5 ± 13.2	67.2 ± 17.6
Male/female (n)	8/5	6/5	10/4	7/6
E/A/L	7/6/0	6/5/0	2/1/11	1/1/11
BP (mm Hg)				
Systolic	158.1 ± 10.3	171.0 ± 8.6	181.6 ± 8.7	182.2 ± 8.7
Diastolic	78.0 ± 3.6	90.2 ± 6.0	96.9 ± 5.8	90.8 ± 6.0
NIHSS	10.9 ± 2.5	12.5 ± 2.8	5.4 ± 1.3	6.7 ± 3.7
Clinical biochemistry				
CRP (mg/dl)	2.0 ± 1.0	2.5 ± 1.3	0.5 ± 0.3	1.2 ± 0.5
LDH (mg/dl)	231 ± 15.8	261.3 ± 25.2	228.9 ± 23.6	280.3 ± 41.9
TG (mg/dl)	98.4 ± 15.7	100.6 ± 13.2	120.8 ± 16.3	86.2 ± 20.3
TC (mg/dl)	151.7 ± 7.6	151.1 ± 11.3	196.5 ± 13.4	188.8 ± 16.7
LDL (mg/dl)	125.4 ± 6.4	131.0 ± 10.8	175.1 ± 46.5	171.6 ± 18.8
HDL (mg/dl)	42.3 ± 3.4	44.6 ± 3.1	46.5 ± 3.0	42.2 ± 2.9
BG (mg/dl)	116.2 ± 8.1	125.0 ± 3.7	127.7 ± 7.2	154.2 ± 35.3
BUN (mg/dl)	15.6 ± 1.1	18.6 ± 3.4	13.2 ± 0.9	15.7 ± 1.1
CRN (mg/dl)	0.8 ± 0.1	1.0 ± 0.1	0.7 ± 0.1	0.8 ± 0.1

E, cardioembolic; A, atherothrombotic; L, lacunar infarction; BP, blood pressure; TC, total cholesterol; BG; blood glucose; CRN, creatine.